UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,286	01/29/2007	Dirk Beher	T1615YP	4169

210 7590 03/04/2010

MERCK
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
JAVANMARD, SAHAR	

ART UNIT	PAPER NUMBER
1627	

MAIL DATE	DELIVERY MODE
03/04/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/580,286	BEHER ET AL.	
	Examiner	Art Unit	
	SAHAR JAVANMARD	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 5-16* is/are pending in the application.

4a) Of the above claim(s) *13-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/24/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

This Office Action is in response to Applicant's Restriction Requirement remarks filed on October 22, 2009. Claim(s) 1-2 and 5-16 are pending. Claim(s) 13-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant's election of Group I drawn to a method of treating a disease associated with deposition of Aβ in the brain and election of species of compound formula I in which X is S, Y is CH2, Z is CO2H, one R1 group is H and the other is Me, both R2 groups are Me, R3 is 2,5-di-Me-Ph, one of R4, R5 or R6 is 5-isopropyl and the others are H, and R7 4-CF3-Ph (page 10, the sixth compound of table 1) and the disease is Alzheimer's disease with traverse of the restriction requirement in the reply is acknowledged.

The traversal is on the grounds that Applicants submit that unity of invention is present.

Examiner respectfully notes that (MPEP 1801):

> *"An international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to a group of inventions claimed in an international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" is defined in PCT Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any). Whether or not*

> *any particular technical feature makes a "contribution" over the prior art, and therefore constitutes a "special technical feature," should be considered with respect to novelty and inventive step. For example, a document discovered in the international search shows that there is a presumption of lack of novelty or inventive step in a main claim, so that there may be no technical relationship left over the prior art among the claimed inventions involving one or more of the same or corresponding special technical features, leaving two or more dependent claims without a single general inventive concept. Lack of unity of invention may be directly evident "a priori," that is, before considering the claims in relation to any prior art, or may only become apparent "a posteriori," that is, after taking the prior art into consideration. For example, independent claims to A +X, A + Y, X + Y can be said to lack unity a priori as there is no subject matter common to all claims. In the case of independent claims to A + X and A + Y, unity of invention is present a priori as A is common to both claims. However, if it can be established that A is known, there is lack of unity a posteriori, since A (be it a single feature or a group of features) is not a technical feature that defines a contribution over the prior art."*

The requirement is deemed proper and is therefore made FINAL. Claim(s) 1-2 and 5-12 are examined herein insofar as they read on the elected invention and species.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 5-12 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the treatment of disease associated with Aβ deposition, does not reasonably provide enablement for the prevention of disease associated with Aβ deposition as recited in these claims.

The instant claims are drawn to a pharmaceutical composition and a method for the prevention of disease associated with Aβ deposition. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:
(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention:

The instant invention pertains to a method for the prevention of disease associated with Aβ deposition.

The state of the prior art:

The skilled artisan would view that the prevention of one or more symptoms of disease associated with Aβ deposition totally, absolutely, or permanently, is highly unlikely, since one cannot guarantee that the disease will always be prevented.

The relative skill of those in the art:

The relative skill of those in the art is very high.

The predictability or lack thereof in the art:

The skilled artisan would view that the treatment to prevent a disease associated with Aβ deposition, absolutely, or permanently is highly unpredictable.

The amount of direction or guidance presented and the presence or absence of working examples:

In the instant case, no working examples are presented in the specification as filed showing how to prevent disease associated with Aβ deposition totally, absolutely, or permanently. Note that lack of a working example, is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164.

Genentech, Inc. v. Novo Nordisk, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, e.g., the amount of direction or guidance provided, absence of working examples, and the predictability of the art discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test the combination in the instant claims whether preventing disease associated with Aβ deposition totally, absolutely, or permanently.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 5-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing beta-amyloid activity *in vitro*, does not reasonably provide enablement for *in vivo* beta-amyloid activity reduction and thereby treating all disorder associated with Aβ deposition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of

working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of treatment and/or prevention of all disorders related to beta-amyloid deposition comprising administering a compound of formula I. The nature of the invention is complex in that it encompasses the treatment of all types of disorders associated with Aβ deposition.

(2).Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass inhibition of any number of disorders.

(3).Guidance of the Specification:

The language of the claims is not limited to *in vitro* treatments and encompasses treating subjects *in vivo* and as such does not have support in the specification. There is insufficient disclosure to reasonably predict that the methods and compositions of the instant specification would inhibit beta-amyloid activity *in vivo*. This is merely an unsubstantiated assertion with no evidence to support the contention that the *in vitro* studies of the specification are indicative of *in vivo* activity. Applicant has only shown the reduction of the production of Aβ *in vitro* based on cell-based γ-secretase assays, not

treating warm-blooded animals with the claimed inhibitors or shown an art recognized correlation between the data shown and the scope of the claimed invention. The artisan would recognize and appreciate that there is no known correlation between *in vitro* and *in vivo* results, because the artisan recognizes that an *in vitro* assay cannot duplicate the complex conditions of *in vivo* therapy. In the *in vitro* assay, the inhibitor of formula I is present during the entire exposure period. This is not the case *in vivo* where target site exposure may be delayed or inadequate. In addition, variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect. In addition, the composition may not reach the target cells because of its inability to penetrate tissues or cells where its activity is to be exerted, may be absorbed by fluids, cells, and tissues where the composition has no effect and/or a large enough local concentration may not be established. There are no specific teachings in the disclosure that would allow one to have a reasonable expectation of success in transferring the *in vitro* method to treat warm-blooded animals suffering from any disease associated with Aβ deposition. One is only left with speculation and an invitation to experiment. Therefore, the claimed invention lacks an enabling disclosure.

(4).Working Examples:

Applicant has demonstrated that the instant compounds are able to reduce the production of Aβ *in vitro* based on cell-based γ-secretase assays.

(5).State of the Art.

It is well-known in the state of the art that the cause of Alzheimer's disease, by way of example, is multifactorial, that is, there are several factors whose combined effects produce Alzheimer's disease. Alzheimer's disease may result from age related changes, family history, inflammation in the brain etc. These conditions are caused by various etiologies. For example, Alzheimer's disease may be due to neuron loss in the central nervous system or due to deposition of beta-amyloid plaques in the brain. The current known treatment of Alzheimer's disease depends on the patient populations and the severity of the disorder. The underlying cause of Alzheimer's i.e. what actually triggers the changes in the brain is still not known. It is likely that no single factor is responsible, but rather that it is due to a variety of factors, which may differ from person to person. Thus, the state of the art with respect to treatment of all diseases associated with Aβ deposition is very low.

(6).Predictability of the Art.

Despite the advanced training in the medical treatment arts, the arts are highly unpredictable. The state of the art is such that it is not possible to predict the activity of a compound, whether *in vitro* or *in vivo*, based on the structure alone. In order to predict the *in vivo* activity of a compound based on the *in vitro* assay, the assay itself must be definitively well correlated to the pathophysiology of a target disease and verified as being predictive of the *in vivo* activity of a compound. For example, if a receptor is known to be overactivated in the pathophysiology of a disease, the ordinary practitioner

would predict that a compound that inhibits the activation of the receptor may be useful for the treatment of said disease. However, even for *in vitro* models that involve receptors known to be involved in the pathophysiology of a disease, translating the *in vitro* efficacy of the compound to *in vivo* efficacy for the treatment of a disease is notoriously unpredictable unless the correlation has been conclusively verified. Further, the *in vivo* efficacy of a compound is not only determined by the affinity or activity of the compound on its target receptor in a validated in vitro assay, but by a range of other factors including the bioavailability of the compound, its pharmacokinetic profile, and the specificity of the compound for the desired target versus other potential targets.

It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(7). The Quantity of Experimentation Necessary.

In order to practice the claimed invention, one of skill in the art would have to first envision a combination of an appropriate pharmaceutical carrier, a dosage for each compound, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the combination in the model system to determine whether or not the combination is effective for treatment of all disorders related to beta-amyloid deposition. If unsuccessful, which is likely given the lack of significant guidance from the

specification or prior art regarding treatment of disorders related to beta-amyloid deposition with a compound of formula I, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above and test the system again. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat disorders related to beta-amyloid depoaiton by administration of a a compound of formula I as set forth in the claims.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, a method for treatment and /or prevention of any disease associated with Aβ deposition, generally by administering a compound of formula I of the claims is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2 and 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillard (US Patent No. 5,081,138) of record in view of Klegeris (*Neurobiology of Aging*, 2002).

Gillard teaches compounds of formula I which encompass Applicant's elected compound of formula I, in which X is S, both R2 are H, n is 2, E is CO2H, one R1 group is H and the other is Me, both R2 groups are Me, R3 is 2,5-di-Me-Ph, one of R4, R5 or R6 is 5-isopropyl and the others are H, R7 is 4-CF3-Ph, and R8 is H . The compounds are taught to be inhibitors of the biosynthesis of 5-lipoxygenase metabolites of arachidonic acid. Gillard teaches that the compounds are useful as anti-asthmatic, anti-allergic, anti-inflammatory, and cytoprotective agents. The compounds are also useful in treating diarrhea, hypertension, angina, platelet aggregation, cerebral spasm, premature

labor, spontaneous abortion, dysmenorrhea, and migraine (abstract; column 1, lines 55-column 6, line 17).

Gillard does not teach administering said compounds for the treatment of diseases associated with deposition of Aβ in the brain, namely Alzheimer's disease.

Klegeris teaches that neuroinflammation and oxidative stress are believed to be contributing factors to neurodegeneration in normal aging, as well as in age-related neurological disorders. Reactive microglia are found in increased numbers in aging brain and are prominently associated with lesions in such age-related degenerative conditions as Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). In vitro, stimulated microglia or microglial-like cells secrete neurotoxic materials and are generators of free radicals through their respiratory burst system. Agents that suppress microglial activation are therefore candidates for neuroprotection.

Klegeris teaches quantitative in vitro assays for measuring neurotoxicity of microglia or other mononuclear phagocytes were examined.

Klegeris teaches inhibitors of the cyclooxygenase (COX) or the 5-lipoxygenase (5-LOX) pathways as possible neuroprotective agents were tested, namely MK-886 (encompassed by Applicant's compound of formula I) as the 5-LOX activating protein (FLAP) inhibitor.

Klegeris teaches that results show that inhibitors of the 5-LOX pathway have similar effects to inhibitors of the COX pathway in suppressing toxic functions of activated human monocytic THP-1 cells, which were used as a model for human

microglia/macrophages. The specific 5-LOX inhibitor REV 5901 and the FLAP inhibitor MK-886 both reduced neurotoxic secretions of monocytic THP-1 cells in a dose dependent fashion.

It would have been obvious to one of ordinary skill in the art at the time of the invention to have employed the compounds of formula I which are known to be 5-lipoxygenase inhibitors useful in the treatment of anti-asthmatic, anti-allergic, anti-inflammatory, cytoprotective agents, and platelet aggregation among others as taught by Gillard and also employed said compounds for the treatment of Alzheimer's disease. The motivation, provided by Klegeris, teaches that 5-LOX inhibitor, MK-886, which is encompassed by Applicant's compound of formula I, possesses neuroprotective properties in the *in vivo* suppression of microglia/macrophages which indicates that such compounds, with a reasonable degree of success, would be useful in the treatment of neurological disorders such as Alzheimer's disease.

Conclusion

Claims 1-2 and 5-12 are not allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sahar Javanmard whose telephone number is (571) 270-3280. The examiner can normally be reached on 8 AM-5 PM MON-FRI (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/S. J./

Examiner, Art Unit 1627

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627